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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
GOLDBERG, JEANINE ANNE

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 11/21/2002

12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/823,257	LANDERS, JOHN E.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-64* is/are pending in the application.

4a) Of the above claim(s) *29-64* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed August 26, 2002. Currently, claims 1-64 are pending. Claims 60-64 have been withdrawn as drawn to non-elected subject matter.

Election/Restrictions

2. Applicant's election of Group I (Claims 1-59) in Paper No. 11 is acknowledged.

3. Upon further consideration and initial search, the examiner determined that previous Group I was four different methods of haplotying.

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-28, drawn to methods of haplotyping two SNPs by capturing at least one SNP, classified in class 435, subclass 6.

II. Claims 29-39, drawn to haplotyping two or more SNPs by detecting the first and separating based upon the first SNP and analyzing a second SNP, classified in class 435, subclass 6.

III. Claims 40-48, drawn to methods of haplotyping by using four labeled probes, classified in class 435, subclass 6.

IV. Claims 49-59, drawn to methods of haplotyping using four different hybridization reactions and energy transfer, classified in class 435, subclass 6.

V. Claim60-64, drawn to kits comprising two sets of ASO probes, classified in class 536, subclass 24.3.

The inventions of Group I-IV are patentably distinct methods because they each have different reagents and different method steps. The method of Group I uses capture to identify the haplotype. Group II uses serial analysis for identifying haplotypes. Group III uses four different labeled probes for determining a haplotype. Alternatively, the method of Group IV uses four different hybridization reactions and energy transfer. Therefore the methods are distinct over one another. A search of one group is not coextensive of each of the other groups since they require different features which are not relied upon in the other groups.

With respect to applicant's traversal of the originally presented restriction, the response asserts that the entire application may be searched without undue burden on the examiner. This argument has been reviewed, but found not convincing because the claims are separately classified, a prima facie case for burden of search. Moreover, as provided in the restriction requirement, the claims are distinct for the reasons stated. The response has provided not technical arguments why the search would not be a burned. Therefore, the requirement is still deemed proper and is therefore made FINAL.

Claims 60-64 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

During a telephone conversation with Helen Lockhart on November 12, 2002 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-28. Affirmation of this election must be made by applicant in replying to this

Office action. Claims 29-64 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Priority

4. This application claims priority to provisional application 60-194,425, filed April 4, 2000.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim*** rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A)

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in-

(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

6. Claims 1-4, 6-7, 11-14, 16, 18-23, 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Cronin et al (Human Mutation, Vol. 7, pages 244-255, 1996).

Cronin et al. (herein referred to as Cronin) teaches a method of detecting mutations using hybridization to a light-generated DNA probe array. Cronin teaches an array of 1480 probes chosen to detect known deletions, insertions or base substitution mutations (abstract). Cronin teaches the arrays are highly effective in analyzing complex mutation and polymorphism patterns (abstract). The mutation arrays of Cronin are composed of two parallel probe sets, one set complementary to the wild-type gene sequence and the other complementary to a given mutant sequence. The format of the array enables specific, highly parallel CFTR mutation analysis for homozygous and heterozygous genomic samples even in the context of other local polymorphisms (page 246, col. 1)(limitations of Claim 14, 19, 22). The mutational array comprises probes for each of 37 CFTR mutations in specific sets of probes (limitations of Claim 20-21). Cronin teaches fluorescein labeling oligonucleotide targets (page 246, col. 2)(limitations of Claim 18). DNA was prepared from genomic DNA by amplification (col. 247, col. 1)(limitations of Claim 16-17, 27). Methods which amplify genomic DNA samples prior to application to the array have reduced the complexity of the genome. The

hybridization was detected by fluorescent image generation. Cronin teaches that several DNA samples were analyzed to determine the haplotype, identity at more than one SNP. Using a mutation specific probe array, "one sample was compound heterozygous for G480C (G-T) in exon 10 and G551D (G-A) in exon 11 (page 251, col. 1). As seen in Figure 4, images of the mutation specific array are provided to illustrate the presence of mutations. Table 1, page 253 demonstrates the cystic fibrosis mutation-specific DNA probe array (page 253). Table 2 provides results for analysis of patients samples using the CFTR genotyping. With respect to Claim 12, each ASO corresponding to an allele of the second SNP is hybridized independently to the sample because each location on the array is a discrete location, therefore, each site is independently hybridized to the nucleic acid sample. Therefore, Cronin teaches a method of analyzing two polymorphic loci on a solid support.

7. Claims 1-4, 6-7, 11, 14, 16, 18-19, 22-23, 25-28 are rejected under 35 U.S.C. 102(e) as being anticipated by Gentalen et al. (US Pat. 6,306,643, October 2001).

Gentalen teaches a method of using an array of probes in genetic analysis. Gentalen teaches methods which use multiple cells in an array containing different pooled mixtures of probes. Gentalen provides an example which detects a target nucleic acid having two polymorphic sites, each of which has two polymorphic forms (A/a and B/b). Four combinations of the probes exist (AB, aB, ab, Ab). The target sequence is analyzed by designing four cells each containing a different pool of two

mixed probes. The pool of probes having both component probes matched with the target nucleic acid shows the highest binding (col. 9, lines 40-55)(limitations of Claim 1, 2, 3, 4, 11, 14, 22, 23). The supports typically have discrete spatially addressable regions or cells (col. 11, liens 15-16). (limitations of Claim 6, 7). The target nucleic acid can be genomic, mitochondrial DNA, RNA or cDNA (col. 10, lines 19-20, col. 6, lines 33-34)(limitations of Claim 25-28). The genomic DNA samples are usually subject to amplification before application to an array (col. 10, lines 22-23)(limitations of Claims 16-17). Methods which amplify genomic DNA samples prior to application to the array have reduced the complexity of the genome.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 5, 9-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cronin et al (Human Mutation, Vol. 7, pages 244-255, 1996) in view of Newton (U.S. Patent 5,525,494, June 11, 1996).

Cronin et al. (herein referred to as Cronin) teaches a method of detecting mutations using hybridization to a light-generated DNA probe array. Cronin teaches an array of 1480 probes chosen to detect known deletions, insertions or base substitution

mutations (abstract). Cronin teaches the arrays are highly effective in analyzing complex mutation and polymorphism patterns (abstract). The mutation arrays of Cronin are composed of two parallel probe sets, one set complementary to the wild-type gene sequence and the other complementary to a given mutant sequence. The format of the array enables specific, highly parallel CFTR mutation analysis for homozygous and heterozygous genomic samples even in the context of other local polymorphisms (page 246, col. 1)(limitations of Claim 14, 19, 22). The mutational array comprises probes for each of 37 CFTR mutations in specific sets of probes (limitations of Claim 20-21). Cronin teaches fluorescein labeling oligonucleotide targets (page 246, col. 2)(limitations of Claim 18). DNA was prepared from genomic DNA by amplification (col. 247, col. 1)(limitations of Claim 16, 27). The hybridization was detected by fluorescent image generation. Cronin teaches that several DNA samples were analyzed to determine the haplotype, identity at more than one SNP. Using a mutation specific probe array, "one sample was compound heterozygous for G480C (G-T) in exon 10 and G551D (G-A) in exon 11 (page 251, col. 1). As seen in Figure 4, images of the mutation specific array are provided to illustrate the presence of mutations. Table 1, page 253 demonstrates the cystic fibrosis mutation-specific DNA probe array (page 253). Table 2 provides results for analysis of patients samples using the CFTR genotyping.

Cronin does not specifically teach detecting SNP using a multiwell dish. Cronin does not specifically teach using a spacer sequence to attach the probe to the solid support.

However, Newton teaches oligonucleotides are immobilized to a microtitre dish (a multiwell dish) for analysis of SNPs (limitations of Claim 5). Newto teaches attaching probes to a solid phase via an amino link on the 5' end of the final T of the poly T region (col. 11, lines 60-65)(limitations of Claim 9-10).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to have modified the method of detecting numerous SNPs using an array with the teachings of Newton that an array of nucleic acids may be analyzed in separate wells of a multiwell dish. Additionally, the ordinary artisan would have recognized that probes may be attached to solid support via an amino link on the 5' end of the final T of the poly T region. Therefore, the ordinary artisan would have been motivated to have added the polyT tail to enable attachment to the solid support.

9. Claims 5, 12-13, 25-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cronin et al (Human Mutation, Vol. 7, pages 244-255, 1996) in view of Walt et al. (U.S. Patent 6,327,410, December 4, 2001).

Cronin et al. (herein referred to as Cronin) teaches a method of detecting mutations using hybridization to a light-generated DNA probe array. Cronin teaches an array of 1480 probes chosen to detect known deletions, insertions or base substitution mutations (abstract). Cronin teaches the arrays are highly effective in analyzing complex mutation and polymorphism patterns (abstract). The mutation arrays of Cronin are composed of two parallel probe sets, one set complementary to the wild-type gene sequence and the other complementary to a given mutant sequence. The format of the

array enables specific, highly parallel CFTR mutation analysis for homozygous and heterozygous genomic samples even in the context of other local polymorphisms (page 246, col. 1)(limitations of Claim 14, 19, 22). The mutational array comprises probes for each of 37 CFTR mutations in specific sets of probes (limitations of Claim 20-21). Cronin teaches fluorescein labeling oligonucleotide targets (page 246, col. 2)(limitations of Claim 18). DNA was prepared from genomic DNA by amplification (col. 247, col. 1)(limitations of Claim 16, 27). The hybridization was detected by fluorescent image generation. Cronin teaches that several DNA samples were analyzed to determine the haplotype, identity at more than one SNP. Using a mutation specific probe array, "one sample was compound heterozygous for G480C (G-T) in exon 10 and G551D (G-A) in exon 11 (page 251, col. 1). As seen in Figure 4, images of the mutation specific array are provided to illustrate the presence of mutations. Table 1, page 253 demonstrates the cystic fibrosis mutation-specific DNA probe array (page 253). Table 2 provides results for analysis of patients samples using the CFTR genotyping. Therefore, Cronin teaches a method of analyzing two polymorphic loci on a solid support.

Cronin does not specifically teach using surfaces such as multiwell dishes and beads. Cronin does not specifically teach that the sample may be RNA or cDNA.

However, Walt teaches a method of detecting target analytes using a surface which has been modified to contain physical configurations such as wells or small depressions in the substrate that can retain the beads such that a microsphere can rest in the well (col. 5, lines 60-65). As seen in Figure 5A and 5B, beads are located within a welled dish. Walt teaches that bioactive agents include nucleic acids. The nucleic acid

may be DNA, both genomic and cDNA, RNA or any combination (col. 10, lines 30-33). Walt teaches that probes are designed to be complementary to a target sequence such that hybridization of the target and the probes of the present invention occurs (col. 10, lines 40-50). Each bead comprises a single type of bioactive agent (col. 11, lines 40-50). Walt teaches using different dyes which allow for distinguishing between molecules (col. 13). Walt teaches that the methodology finds uses in detection of mutations or mismatches in target nucleic acids such as single nucleotide polymorphisms (col. 24, lines 53-60). Walt teaches that the use of the beads with bioactive agents allows the beads to be randomly distributed on the array, a fast and inexpensive process as compared to either the in situ synthesis or spotting techniques of the prior art (col. 4, lines 53-56).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to have modified the array surface of Cronin to contain wells and beads as taught by Walt. The ordinary artisan would have been motivated to have designed the array surface according to Walt since Walt teaches that "the use of the beads with bioactive agents allows the beads to be randomly distributed on the array, a fast and inexpensive process as compared to either the in situ synthesis or spotting techniques of the prior art" (col. 4, lines 53-56). Additionally, Walt teaches that any nucleic acid may be detected. Therefore, the ordinary artisan would have recognized that detection of nucleic acids on a solid support may include both RNA and cDNA for the added flexibility of the method.

10. Claims 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cronin et al (Human Mutation, Vol. 7, pages 244-255, 1996) in view of Arnold et al. (U.S. Patent 6,410,231, June 25, 2002).

Cronin et al. (herein referred to as Cronin) teaches a method of detecting mutations using hybridization to a light-generated DNA probe array. Cronin teaches an array of 1480 probes chosen to detect known deletions, insertions or base substitution mutations (abstract). Cronin teaches the arrays are highly effective in analyzing complex mutation and polymorphism patterns (abstract). The mutation arrays of Cronin are composed of two parallel probe sets, one set complementary to the wild-type gene sequence and the other complementary to a given mutant sequence. The format of the array enables specific, highly parallel CFTR mutation analysis for homozygous and heterozygous genomic samples even in the context of other local polymorphisms (page 246, col. 1)(limitations of Claim 14, 19, 22). The mutational array comprises probes for each of 37 CFTR mutations in specific sets of probes (limitations of Claim 20-21). Cronin teaches fluorescein labeling oligonucleotide targets (page 246, col. 2)(limitations of Claim 18). DNA was prepared from genomic DNA by amplification (col. 247, col. 1)(limitations of Claim 16, 27). The hybridization was detected by fluorescent image generation. Cronin teaches that several DNA samples were analyzed to determine the haplotype, identity at more than one SNP. Using a mutation specific probe array, "one sample was compound heterozygous for G480C (G-T) in exon 10 and G551D (G-A) in exon 11 (page 251, col. 1). As seen in Figure 4, images of the mutation specific array are provided to illustrate the presence of mutations. Table 1, page 253 demonstrates

the cystic fibrosis mutation-specific DNA probe array (page 253). Table 2 provides results for analysis of patients samples using the CFTR genotyping. Therefore, Cronin teaches a method of analyzing two polymorphic loci on a solid support.

Cronin does not specifically teach suing four different labels for each of the ASO probes.

However, Arnold teaches methods of detecting single nucleotide polymorphisms (SNPs) by capturing probes which contain different labels. Arnold provides an example for simultaneously probing for n different SNPs on a target with m alleles each exploits nxm differentially detectable labels. For example, for two SNPs each with two alleles, this embodiment exploit four differentially detectable labels measures as for instance, a Cy2/Cy7 ration for one SNP and a Cy3/Cy5 for the second SNP (col. 5, lines 35-45)(limitations of Claim 15).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to have modified the detection method of Cronin with the teachings of Arnold to detect SNPs by using differential labels. The ordinary artisan would have been motivated to have used different labels for each distinct allele assayed for the expected benefit of ease of detection and definitive detection.

Conclusion

11. No claims allowable over the art.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J. Goldberg

Jeanine Goldberg
November 15, 2002

W. Gary Jones
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